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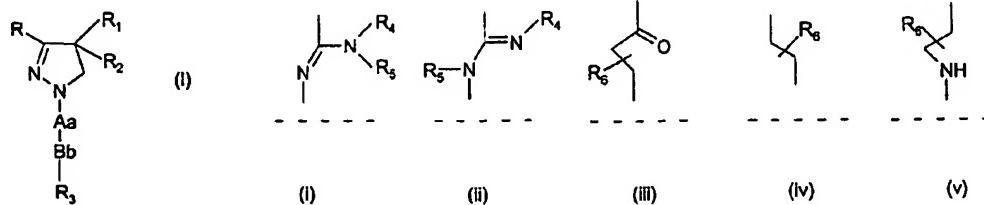
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(54) Title: 4,5-DIHYDRO-1H-PYRAZOLE DERIVATIVES HAVING CB₁-ANTAGONISTIC ACTIVITY

WO 01/70700 A1



(57) Abstract: The present invention relates to a group of novel 4,5-dihydro-1H-pyrazole derivatives which are potent antagonists of the cannabis CB₁-receptor. The compounds have general formula (I) wherein R and R₁ are the same or different and represent phenyl, thiienyl or pyridyl which groups may be substituted with 1, 2 or 3 substituents Y or R and/or R₁ represent naphthyl, R₂ represents hydrogen, hydroxy, C₁₋₃-alkoxy, acetoxy or propionyloxy, Aa represents one of the groups (i), (ii), (iii), (iv) or (v), Bb represents sulfonyl or carbonyl, R₃ represents benzyl, phenyl, thiienyl or pyridyl which may be substituted with 1, 2 or 3 substituents Y or R₃ represents C₁₋₈ branched or unbranched alkyl or C₃₋₈ cycloalkyl, or R₃ represents naphthyl.

4,5-Dihydro-1H-pyrazole derivatives having CB₁-antagonistic activity

The present invention relates to a group of novel 4,5-dihydro-1H-pyrazole derivatives, to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.

5 The above mentioned 4,5-dihydro-1H-pyrazoles are potent Cannabis-1 (CB₁) receptor antagonists with utility for the treatment of psychiatric and neurological disorders.

10 Cannabinoids are present in the Indian hemp *Cannabis Sativa L.* and have been used as medicinal agents for centuries (Mechoulam, R.; Feigenbaum, J.J. *Prog. Med. Chem.* 1987, 24, 159). However, only within the past ten years the research in the cannabinoid area has revealed pivotal information on cannabinoid receptors and their (endogenous) agonists and antagonists. The discovery and the subsequent cloning of two different subtypes of Cannabinoid receptors (CB₁ and CB₂) stimulated the search for novel cannabinoid receptor antagonists (Munro, S.; Thomas, K.L.; Abu-Shaar, M. *Nature* 1993, 365, 61. Matsuda, L.A.; Bonner, T.I. *Cannabinoid Receptors*, Pertwee, R.G. Ed. 1995, 117, Academic Press, London).

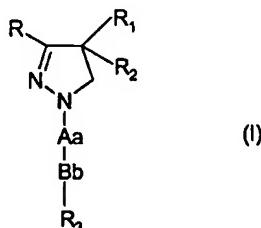
15 In addition, pharmaceutical companies became interested in the development of cannabinoid drugs for the treatment of diseases connected with disorders of the cannabinoid system. The wide distribution of CB₁ receptors in the brain, in combination with the strictly peripheral localisation of the CB₂ receptor, makes the CB₁ receptor a very interesting molecular target for CNS-directed drug discovery

20 in the areas of both psychiatric and neurological disorders (Consroe, P. *Neurobiology of Disease* 1998, 5, 534. Pop, E. *Curr. Opin. In CPNS Investigational Drugs* 1999, 1, 587. Greenberg, D.A. *Drug News Perspect.* 1999, 12, 458). Hitherto, three types of distinct CB₁ receptor antagonists are known. Sanofi disclosed their diarylpyrazole congeners as selective CB₁ receptor antagonists. A representative example is SR-141716A, which is currently undergoing Phase II clinical development for psychotic disorders (Dutta, A.K.; Sard, H.; Ryan, W.; Razdan, R.K.; Compton, D.R.; Martin, B.R. *Med. Chem. Res.* 1994, 5, 54. Lan, R.; Liu, Q.; Fan, P.; Lin, S.; Fernando, S.R.; McCallion, D.; Pertwee, R.; Makriyannis, A. *J. Med. Chem.* 1999, 42, 769. Nakamura-Palacios, E.M.; Moerschbaecher, J.M.; Barker, L.A. *CNS Drug Rev.* 1999, 5, 43).

25 Aminoalkylindoles have been disclosed as CB₁ receptor antagonists. A representative example is Iodopratadoline (AM-630), which was introduced in 1995. AM-630 is a CB₁ receptor antagonist, but sometimes behaves as a weak

partial agonist (Hosohata, K.; Quock, R.M.; Hosohata, Y.; Burkey, T.H.; Makriyannis, A.; Consroe, P.; Roeske, W.R.; Yamamura, H.I. *Life Sc.* 1997, 61, PL115). More recently, researchers from Eli Lilly described aryl-aryl substituted benzofurans as selective CB₁ receptor antagonists (e.g. LY-320135) (Felder, C.C.; Joyce, K.E.; Briley, E.J.; Glass, M.; Mackie, K.P.; Fahey, K.J.; Cullinan, G.J.; Hunden, D.C.; Johnson, D.W.; Chaney, M.O.; Koppel, G.A.; Brownstein, M. *J. Pharmacol. Exp. Ther.* 1998, 284, 291). Recently, 3-alkyl-5,5'-diphenylimidazolidinediones were described as cannabinoid receptor ligands, which were indicated to be cannabinoid antagonists (Kanyonyo, M.; Govaerts, S.J.; Hermans, E.; Poupaert, J.H., Lambert, D.M. *Bioorg. Med. Chem. Lett.* 1999, 9, 2233). Interestingly, many CB₁ receptor antagonists have been reported to behave as inverse agonists *in vitro* (Landsman, R.S.; Burkey, T.H.; Consroe, P.; Roeske, W.R.; Yamamura, H.I. *Eur. J. Pharmacol.* 1997, 334, R1). Recent reviews provide a nice overview of the current status in the cannabinoid research area (Mechoulam, R.; Hanus, L.; Fride, E. *Prog. Med. Chem.* 1998, 35, 199. Lambert, D.M. *Curr. Med. Chem.* 1999, 6, 635. Mechoulam, R.; Fride, E.; Di Marzo, V. *Eur. J. Pharmacol.* 1998, 359, 1).

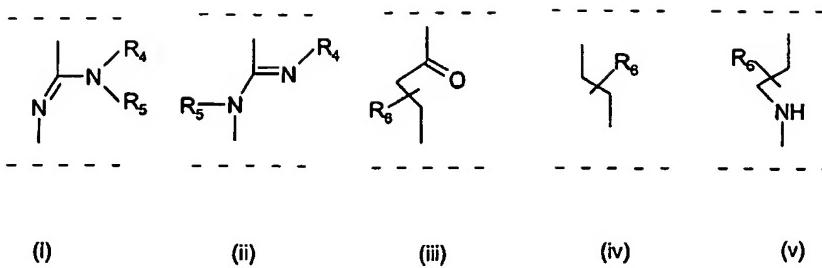
It has now surprisingly been found that the novel 4,5-dihydro-1H-pyrazole derivatives of the formula (I), prodrugs thereof, tautomers thereof and salts thereof



wherein

- R and R₁ are the same or different and represent phenyl, thienyl or pyridyl which groups may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, from the group C₁₋₃-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C₁₋₂)-amino, mono- or dialkyl (C₁₋₂)-amido, (C₁₋₃)-alkyl sulfonyl, dimethylsulfamido, C₁₋₃-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R and/or R₁ represent naphtyl,
- R₂ represents hydrogen, hydroxy, C₁₋₃-alkoxy, acetoxy or propionyloxy,
- Aa represents one of the groups (i), (ii), (iii), (iv) or (v)

3



(I) (ii) (iii) (iv) (v)

wherein

- R₄ and R₅ independently of each other represent hydrogen or C₁₋₈ branched or unbranched alkyl or C₃₋₈ cycloalkyl or R₄ represents acetamido or dimethylamino or 2,2,2-trifluoroethyl or phenyl or pyridyl with the proviso that R₅ represents hydrogen
- R₆ represents hydrogen or C₁₋₃ unbranched alkyl

- Bb represents sulfonyl or carbonyl,
- R₃ represents benzyl, phenyl, thienyl or pyridyl which may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, or R₃ represents C₁₋₈ branched or unbranched alkyl or C₃₋₈ cycloalkyl, or R₃ represents naphtyl

are potent and selective antagonists of the cannabis CB₁-receptor.

Due to the potent CB₁ antagonistic activity the compounds according to the invention are suitable for use in the treatment of psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite disorders, obesity, neurological disorders such as dementia, dystonia, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, as well as for the treatment of pain disorders and other CNS-diseases involving cannabinoid neurotransmission, and in the treatment of gastrointestinal disorders and cardiovascular disorders.

The affinity of the compounds of the invention for cannabinoid CB₁ receptors was determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabis CB₁ receptor is stably transfected in conjunction with [³H]CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [³H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid

scintillation counting.

The cannabinoid CB₁ antagonistic activity of compounds of the invention was determined by functional studies using CHO cells in which human cannabinoid CB₁ receptors are stably expressed. Adenylyl cyclase was stimulated using forskolin and measured by quantifying the amount of accumulated cyclic AMP. Concomitant activation of CB₁ receptors by CB₁ receptor agonists (e.g. CP-55,940 or (R)-WIN-55,212-2) can attenuate the forskolin-induced accumulation of cAMP in a concentration-dependent manner. This CB₁ receptor-mediated response can be antagonised by CB₁ receptor antagonists such as the compounds of the invention.

At least one centre of chirality is present (at the C₄ position of the 4,5-dihydro-1H-pyrazole moiety) in the compounds of the formula (I). The invention relates both to racemates, mixtures of diastereomers and the individual stereoisomers of the compounds having formula (I).

The invention also relates both to the E isomer, Z isomer and E/Z mixtures of compounds having formula (I) wherein Aa has the meaning (i) or (ii) as described herein above.

The compounds of the invention can be brought into forms suitable for administration by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

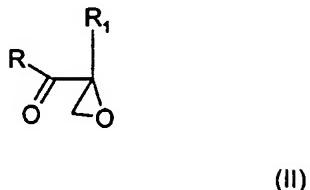
The compounds of the invention having formula (III) (*vide infra*), wherein R₂ represents hydrogen can be obtained according to methods known, for example:
a) EP 0021506; b) DE 2529689.

A suitable synthesis for the compounds according to the present invention is the following:

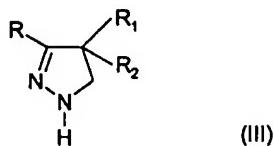
Synthesis route A (for compounds having formula (I), wherein Aa has the meaning (i) or (ii) as described herein above).

Step 1 of route A

Reaction of a compound having formula (II)



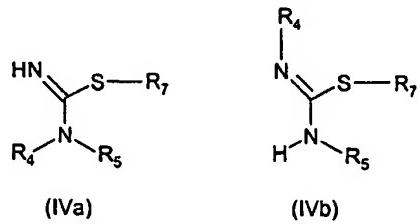
with hydrazine or hydrazine hydrate. This reaction gives a compound having formula (III)



10 wherein R₂ represents a hydroxy group. This reaction is preferably carried out in a polar solvent, such as for example ethanol. Compounds having formula (III) wherein R₂ represents a hydroxy group and wherein R and R₁ have the meaning as described herein above for compound (I) are new.

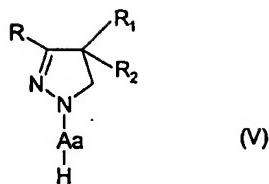
Step 2 of route A

15 Reaction of a compound having formula (III) with a compound having formula (IVa) or a compound having formula (IVb)



wherein R₇ represents a lower alkyl group, such as for example 2-methyl-2-thiopseudourea, or with a suitable salt form thereof in the presence of a base. This reaction gives a 4,5-dihydro-1H-pyrazole-1-carboxamidine derivative having formula (V)

6



wherein Aa has the meaning (i) or (ii) as described herein above. Compounds having formula (V) wherein Aa has the meaning (i) or (ii) as described herein above and wherein R, R₁ and R₂ have the meaning as described herein above for compound (I) are new.

Alternatively, a compound having formula (III) is reacted with a so-called guanylating agent. Examples of such guanylating agents are 1H-pyrazole-1-carboxamidine and its salts (for example the hydrochloride salt) and 3,5-dimethyl-1H-pyrazole-1-carboxamidine and its salts (for example the nitrate salt) and the like. This reaction gives a carboxamidine derivative having formula (V).

Alternatively, a compound having formula (III) is reacted with a so-called protected guanylating agent. Examples of such protected guanylating agents are N-(benzyloxycarbonyl)-1H-pyrazole-1-carboxamidine, N-(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine and N,N'-bis-(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine and the like. This reaction gives after deprotection a compound having formula (V).

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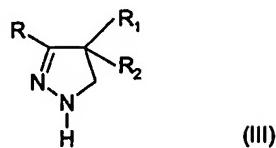
Step 3 of route A

The compound having formula (V) is reacted with an optionally substituted compound of the formula R₃-SO₂X or R₃-COX, wherein R₃ has the above mentioned meaning and X represents a halogen atom. This reaction is preferably carried out in the presence of a base, such as triethylamine in an aprotic solvent, such as acetonitrile. This reaction gives compound (I) wherein Bb represents a sulfonyl group or a carbonyl group, respectively.

Synthesis route A1 (for compounds having formula (I), wherein Aa has the meaning (i) or (ii) as described herein above)

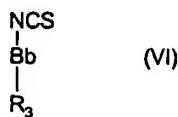
Step 1 of route A1

Reaction of a compound having formula (III)



5

with a thioisocyanate derivative having formula (VI).

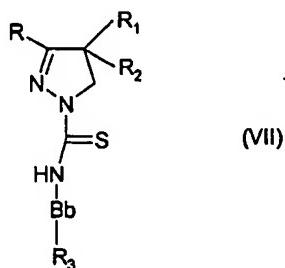


10

This reaction is preferably carried out in an inert organic solvent, such as for example acetonitrile.

This reaction gives a thiocarboxamide derivative having formula (VII). Compounds having formula (VII) wherein R, R₁, R₂, R₃ and Bb have the meaning as described herein above for compound (I) are new.

15

Step 2 of route A1

Reaction of a compound having formula (VII) with an amine in the presence of a mercury(II) salt, such as for example HgCl₂, gives a compound having formula (I) wherein Aa has the meaning (i) or (ii) as described herein above.

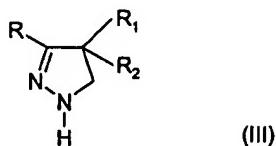
This reaction is preferably carried out in a polar organic solvent, such as for example acetonitrile.

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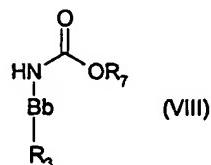
Synthesis route A2 (for compounds having formula (I), wherein Aa has the meaning (i) or (ii) as described herein above)

Step 1 of route A2

Reaction of a compound having formula III



5 with a carbamate ester derivative having formula (VIII).

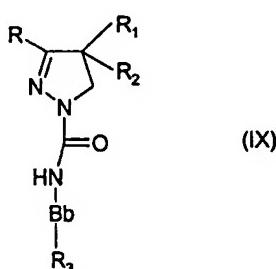


wherein R₇ represents a lower alkyl group, for example methyl.

10 This reaction is preferably carried out in an inert organic solvent, such as for example 1,4-dioxane.

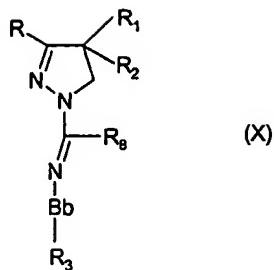
This reaction gives a 4,5-dihydropyrazole-1-carboxamide derivative having formula (IX). Compounds having formula (IX) wherein R, R₁, R₂, R₃ and Bb have the meaning as described herein above for compound (I) are new.

15

Step 2 of route A2

20 Reaction of a compound having formula (IX) with a halogenating agent, such as for example PCl₅, gives a 4,5-dihydropyrazole-1-carboximidoyl halogenide derivative having formula (X)

9



wherein R_8 represents a halogen atom, such as for example chloro. This reaction is preferably carried out in an inert organic solvent, such as for example chlorobenzene.

Compounds having formula (X) wherein R , R_1 , R_2 , R_3 and Bb have the meaning as described herein above for compound (I) and wherein R_8 represents a halogen atom are new.

Step 3 of route A2

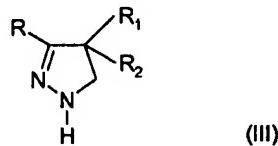
Reaction of a compound having formula (X) with an amine gives a compound having formula (I) wherein Aa has the meaning (i) or (ii) as described herein above.

This reaction is preferably carried out in an inert organic solvent, such as for example dichloromethane.

Synthesis route A3 (for compounds having formula (I), wherein Aa has the meaning (i) or (ii) as described herein above)

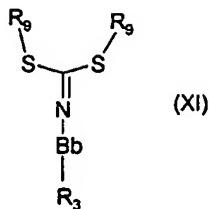
Step 1 of route A3

Reaction of a compound having formula III



with a dithioimidocarbonic ester derivative having formula (XI).

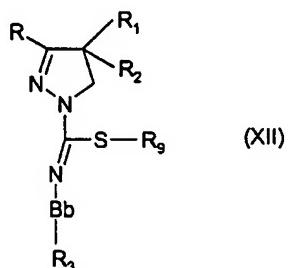
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wherein R₉ represents a C₁₋₃ alkyl group.

This reaction is preferably carried out in a polar organic solvent, such as for example acetonitrile.

This reaction gives a carboximidothioic ester derivative having formula (XII).



wherein R₉ represents a C₁₋₃ alkyl group. Compounds having formula (XII) wherein R, R₁, R₂, R₃ and Bb have the meaning as described herein above for compound (I) and wherein R₉ represents a C₁₋₃ alkyl group are new.

Step 2 of route A3

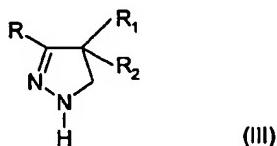
Reaction of a compound having formula (XII) with an amine gives a compound having formula (I) wherein Aa has the meaning (i) or (ii) as described herein above.

This reaction is preferably carried out in a polar organic solvent, such as for example methanol.

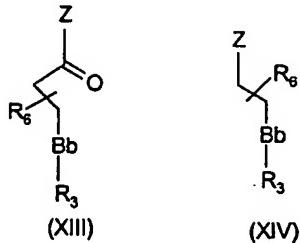
Synthesis route B (for compounds having formula (I), wherein Aa has the meaning (iii) or (iv) as described herein above)

Step 1 of route B

Reaction of a compound having formula (III)



with a compound having formula (XIII), or a compound having formula (XIV), respectively



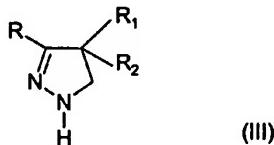
5 wherein Bb, R₃ and R₆ have the above mentioned meanings and Z represents a so-called leaving group.

These reactions give compounds having formula (I), wherein Aa has the meaning (iii) or (iv), respectively.

10 Synthesis route C (for compounds having formula (I), wherein Aa has the meaning (v) as described herein above)

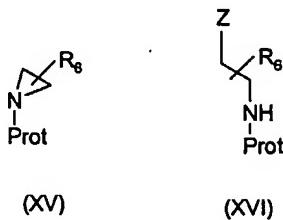
Step 1 of route C

Reaction of a compound having formula (III)



15

with an aziridine derivative having formula (XV), or a compound having formula (XVI), respectively



20

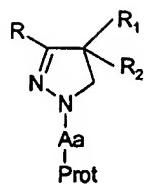
(XV)

(XVI)

wherein R₆ has the above mentioned meaning, Z represents a so-called leaving group and Prot represents a so-called protective group, such as *tert*-butoxycarbonyl, benzyloxycarbonyl and the like.

25 These reactions give compounds having formula (XVII)

12



wherein Aa has the meaning (v) as described herein above. Compounds having formula (XVII) wherein R, R₁ and R₂ have the meaning as described herein above for compound (I) and wherein Aa has the meaning (v) as described herein above and wherein Prot represents a so-called protective group are new.

Subsequent removal of the so-called protective group according to known methods (see for example: T.W. Greene, P.G.M. Wuts, "Protective Groups in Organic Synthesis", third edition, John Wiley & Sons, Inc., New York, 1999) gives compounds (V), wherein Aa has the meaning (v) as described herein above). Compounds having formula (V) wherein R, R₁ and R₂ have the meaning as described herein above for compound (I) and wherein Aa has the meaning (v) as described herein above are new.

Step 2 of route C

The compound having formula (V), wherein Aa has the meaning (v) as described herein above, is reacted with an optionally substituted compound of the formula R₃-SO₂X or R₃-COX, wherein R₃ has the above mentioned meaning and X is halogen. This reaction preferably is carried out in the presence of a base, such as triethylamine in an aprotic solvent, such as acetonitrile. This reaction gives compound (I) wherein Bb represents a sulfonyl group or carbonyl group respectively.

Alternatively, the above mentioned compound having formula (V) can be reacted with a compound of the formula R₃-COOH via formation of an active ester or in the presence of a so-called coupling reagent.

The preparation of the compounds is illustrated in the following examples.

Example I

3-(4-Chlorophenyl)-4,5-dihydro-4-hydroxy-4-phenyl-1H-pyrazole

2-(4-Chlorobenzoyl)-2-phenyloxirane (112 gram, 0.43 mol) is dissolved in ethanol (650 ml) at 35 °C. To the resulting stirred solution is added N₂H₄.H₂O (42 ml) and the formed 3-(4-chlorophenyl)-4,5-dihydro-4-hydroxy-4-phenyl-1H-pyrazole slowly precipitates. After standing for 16 hours the crystalline material is collected by filtration and successively washed with ethanol, water and ethanol and

subsequently dried to give 3-(4-chlorophenyl)-4,5-dihydro-4-hydroxy-4-phenyl-1H-pyrazole (92 gram, 78 % yield). Melting point: 195-196 °C.

Example II

5

3-(4-Chlorophenyl)-4,5-dihydro-N-(4-fluorophenyl)sulfonyl)-4-phenyl-1H-pyrazole-1-carboxamidine

10

Part A: A stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (5.13 gram, 20.0 mmol), 2-methyl-2-thiopseudourea hydroiodide (5.00 gram, 23.0 mmol) and pyridine (10 ml) is heated at 110 °C for 1 hour. After one night standing at room temperature diethyl ether is added and the precipitate is collected by filtration. This precipitate is washed three times with diethyl ether portions to afford a solid (9 gram). Melting point: ~230 °C. This solid is dissolved in methanol (20 ml). To the resulting solution is successively added a 2N sodium hydroxide solution (12 ml) and water (200 ml). The formed precipitate is collected by filtration, washed two times with diethyl ether and successively with diisopropyl ether. The resulting solid is dried *in vacuo* to yield 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (5.1 gram, 88 % yield). Melting point: 187-189 °C.

15

Part B: To a stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (0.50 gram, 1.68 mmol) and 4-fluorophenylsulfonyl chloride (0.34 gram, 1.75 mmol) in acetonitrile (10 ml) is added N,N-dimethyl-4-aminopyridine (0.020 gram, 0.175 mmol) and triethylamine (1 ml). The resulting solution is stirred at room temperature for 30 minutes. After addition of a 2N sodium hydroxide solution and extraction with ethylacetate (400 ml), the ethylacetate layer is concentrated *in vacuo*. The resulting crude residue is further purified by means of flash chromatography (petroleum ether/diethyl ether = 1/1 (v/v), followed by ethylacetate). Subsequent concentration *in vacuo* affords solid 3-(4-chlorophenyl)-4,5-dihydro-N-((4-fluorophenyl)sulfonyl)-4-phenyl-1H-pyrazole-1-carboxamidine (0.55 gram, 72 % yield). Melting point: 214-215 °C

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25

In an analogous manner the compounds having formula (I) listed below have been prepared:

30

4,5-Dihydro-N-((4-fluorophenyl)sulfonyl)-3-(4-methoxyphenyl)-4-(4-methoxy-phenyl)-1H-pyrazole-1-carboxamidine: Melting point: 155-156 °C
4,5-Dihydro-3-(4-methoxyphenyl)-4-(4-methoxyphenyl)-N-((4-methoxy-phenyl)sulfonyl)-1H-pyrazole-1-carboxamidine: Melting point: 148-150 °C

3-(4-Chlorophenyl)-4,5-dihydro-4-phenyl-N-((2,4,6-trimethylphenyl)sulfonyl)-1H-pyrazole-1-carboxamidine: Melting point: 221-222 °C

3-(4-Chlorophenyl)-4,5-dihydro-N-((4-fluorophenyl)sulfonyl)-4-hydroxy-4-phenyl-1H-pyrazole-1-carboxamidine: Melting point: 227-228 °C

5

Example III

3-(4-Chlorophenyl)-4,5-dihydro-N-(1-naphtoyl)-4-phenyl-1H-pyrazole-1-carboxamidine

To a stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (0.75 gram, 2.50 mmol) and 1-naphtoyl chloride (0.4 ml, 2.70 mmol) in acetonitrile (15 ml) is added triethylamine (1ml). The resulting mixture is stirred at room temperature for 1 hour. After addition of a 2N sodium hydroxide solution and extraction with ethylacetate, the ethylacetate layer is concentrated *in vacuo*. The resulting crude residue is further purified by means of flash chromatography (petroleum ether/diethyl ether = 3/1 (v/v), followed by ethylacetate). Subsequent concentration *in vacuo* affords 3-(4-chlorophenyl)-4,5-dihydro-N-(1-naphtoyl)-4-phenyl-1H-pyrazole-1-carboxamidine (0.94 gram, 83 % yield). Melting point: 206-207 °C

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In an analogous manner the compound having formula (I) listed below has been prepared:

3-(4-Chlorophenyl)-4,5-dihydro-4-phenyl-N-(2-pyridoyl)-1H-pyrazole-1-carboxamidine. Melting point: 118 °C (decomposition)

25

Example IV

N¹,N¹-Dimethyl-N²-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine

Part A: A stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (12.0 gram, 46.8 mmol), [(4-chlorophenyl)sulfonyl]dithioimidocarbonic acid dimethyl ester (CAS: 13068-12-7) (9.20 gram, 31.1 mmol) and triethylamine (15 ml) in acetonitrile (200 ml) is heated at reflux temperature for 20 hours. An additional portion of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (12.0 gram, 46.8 mmol) is added and the resulting mixture is heated at reflux temperature for another 16 hours. After concentration *in vacuo*, dichloromethane is added and the resulting solution is washed twice with water and dried over anhydrous Na₂SO₄. After filtration and evaporation *in vacuo* the residue is further purified by flash chromatography (diethyl ether/ petroleum ether = 1/1 (v/v)) to give 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-

pyrazole-1-carboximidothioic acid methyl ester (12.5 gram, 80% yield based on [(4-chlorophenyl)sulfonyl]dithioimidocarbonic acid dimethyl ester) as an amorphous solid.

5 **Part B:** To a stirred mixture of 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboximidothioic acid methyl ester (4.20 gram, 8.30 mmol) in methanol (75 ml) is added dimethylamine (10 ml) and dichloromethane (75 ml) and the resulting solution is stirred at room temperature for 6 hours. Evaporation *in vacuo* and subsequent flash chromatographic purification (diethyl ether/ petroleum ether = 1/1 (v/v), followed by diethyl ether) gives a solid which is further purified by recrystallisation from diisopropyl ether to yield N¹,N¹-dimethyl-N²-((4-chloro-phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-

10 1-carboxamidine (2.63 gram, 63 % yield). Melting point: 182 °C.

15 In an analogous manner the compounds having formula (I) listed below have been prepared:
N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-(3-pyridyl)-1H-pyrazole-1-carboxamidine. Melting point: 101-105 °C.
20 N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-(4-pyridyl)-1H-pyrazole-1-carboxamidine. Melting point: 112-115 °C.
N¹,N¹-Dimethyl-N²-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-hydroxy-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.
25 N-Ethyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-hydroxy-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 183-185 °C..

Example V

N-Methyl-N'-(3-(trifluoromethyl)benzoyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine

30 **Part A:** To 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (5.13 gram, 20.0 mmol) in acetonitrile (80 ml) is added 3-(trifluoromethyl)benzoylisothiocyanate (4.62 gram, 20.0 mmol) at 0 °C and the resulting mixture is stirred for 1 hour. The formed yellow precipitate is collected by filtration and washed with a small portion of acetonitrile and water, respectively, and subsequently dried *in vacuo* to give 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-N-((3-trifluoromethyl) benzoyl)-1H-pyrazole-1-thiocarboxamide (8.26 gram, 85 % yield). Melting point: 180-182 °C.

Part B: To a stirred suspension of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-N-((3-trifluoromethyl)benzoyl)-1H-pyrazole-1-thiocarboxamide (4.88 gram, 10.0 mmol) in acetonitrile (50 ml) is added cold methylamine (5 ml) to give a green solution. After addition of a solution of HgCl₂ (3.0 gram, 11 mmol) in 25 ml acetonitrile, the resulting mixture is stirred for three hours. The precipitate is removed by filtration over hyflo and the filtrate is collected and concentrated *in vacuo*. After addition of ethylacetate and 0.5 N NaOH, the ethylacetate layer is collected, washed with saturated aqueous NaCl solution and dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. Chromatography (dichloromethane/acetone = 9/1 (v/v)) gives N-methyl-N'-(3-(trifluoro-methyl)benzoyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (0.99 gram, 20 % yield) as a foam. Melting point: Amorphous. R_f (Silicagel: Dichloromethane/acetone = 9/1 (v/v)) = 0.3.

Example VI

15 **N-Methyl-N'-(4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine**

Part A: To a solution of N-((4-chlorophenyl)sulfonyl)carbamic acid methyl ester (CAS: 34543-04-9) (2.99 gram, 12.0 mmol) and pyridine (4 ml) in 1,4-dioxane (20 ml) is added 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (3.39 gram, 13.2 mmol) and the resulting mixture is stirred for 4 hours at 100 °C. After concentration *in vacuo* the residue is dissolved in dichloromethane, successively washed with water, 1N HCl and water, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to a volume of 20 ml. Methyl-tert-butyl ether (60 ml) is added and the resulting solution is concentrated to a volume of 20 ml. The formed crystals are collected by filtration and recrystallised from methyl-tert-butyl ether to give 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (4.75 gram, 76 % yield) Melting point: 211-214 °C.

30 Part B: A mixture of 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (3.67 gram, 7.75 mmol) and phosphorus pentachloride (1.69 gram, 8.14 mmol) in chlorobenzene (40 ml) is heated at reflux for 1 hour. After thorough concentration *in vacuo*, the formed N-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboximidoyl chloride is suspended in dichloromethane and reacted with cold methylamine (1.5 ml). After stirring at room temperature for 1 hour, the mixture is concentrated *in vacuo*. The residue is crystallised from diethyl ether to give

N-methyl-N'-(4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (2.29 gram, 61 % yield). Melting point: 96-98 °C (dec.).

- 5 In an analogous manner the compounds having formula (I) listed below have been prepared:
- N-Methyl-N'-(3-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 156-160 °C.
- 10 N-Methyl-N'-(4-chlorophenyl)sulfonyl)-3-(5-chloro-2-thienyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous
- N-Propyl-N'-(4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 129-138 °C.
- 15 N-(2-Propyl)-N'-(4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 110-112 °C.
- N-Methyl-N'-(2-propyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.
- 20 N-(2-Propyl)-N'-(4-chlorophenyl)sulfonyl)-3-(4-pyridyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.
- N¹-Ethyl-N¹-methyl-N²-(4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 184 °C.
- 25 N¹-Ethyl-N¹-methyl-N²-(4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 173-176 °C.
- N¹,N¹-Dimethyl-N²-(4-(trifluoromethyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 195-196 °C.
- 30 N¹,N¹-Dimethyl-N²-(3-methylphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 195-198 °C.
- N¹,N¹-Dimethyl-N²-(3-methoxyphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 204-206 °C.
- N-Ethyl-N'-(4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.
- 35 N-Dimethylamino-N'-(4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 155-159 °C.
- N-Methyl-N'-(4-(trifluoromethyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.
- N¹,N¹-Dimethyl-N²-(2-methylphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 148-151 °C.
- N-Methyl-N'-(2,4-difluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 85 °C.

- N-Acetamido-N'-(4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.
- N-(2,2,2-Trifluoroethyl)-N'-(4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.
- 5 N-(2-Pyridyl)-N'-(4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 142-146 °C.
- N-(4-Pyridyl)-N'-(4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 204-206 °C.
- 10 N-Phenyl-N'-(4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 158-160 °C.

Example VII

3-(4-Chlorophenyl)-1-[3-((4-chlorophenyl)sulfonyl)butanoyl]-4,5-dihydro-4-phenyl-1H-pyrazole

15 To a stirred mixture of 3-((4-chlorophenyl)sulfonyl)butyric acid (1.85 gram, 7.00 mmol), diisopropylethylamine (3 ml) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.50 gram, 15.7 mmol) was added 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (3.00 gram, 11.7 mmol) and the resulting mixture was stirred for 16 hours at room temperature.

20 After concentration *in vacuo* the resulting residue was purified by flash chromatography (petroleum ether/ diethyl ether = 1/2 (v/v), followed by diethyl ether) to give 3-(4-chlorophenyl)-1-[3-((4-chlorophenyl)sulfonyl)butanoyl]-4,5-dihydro-4-phenyl-1H-pyrazole (3.69 gram, 63 % yield) as a diastereomeric mixture. Melting point: amorphous

25 In an analogous manner the compounds having formula (I) listed below have been prepared:

3-(4-Chlorophenyl)-1-[3-(phenylsulfonyl)propanoyl]-4,5-dihydro-4-phenyl-1H-pyrazole. Melting point: 122-123 °C.

30 3-(4-Chlorophenyl)-1-[3-((4-chlorophenyl)sulfonyl)propanoyl]-4,5-dihydro-4-phenyl-1H-pyrazole. Melting point: 178-181 °C.

Example VIII

3-(4-Chlorophenyl)-4,5-dihydro-4-phenyl-1-[2-((3-(trifluoromethyl)phenyl)sulfonyl)ethyl]-1H-pyrazole

35 To a stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (1.7 gram, 6.60 mmol) and collidine (2 ml) in acetonitrile (25 ml) is slowly added a solution of 2-((3-(trifluoromethyl)phenyl)sulfonyl)ethyl chloride (1.5 gram, 5.50 mmol) in acetonitrile (20 ml) and the resulting solution is heated at reflux

temperature for 16 hours. After concentration *in vacuo* the residue is dissolved in ethylacetate and washed with aqueous sodium hydrogencarbonate solution. The resulting ethylacetate layer is successively washed with 1N hydrochloric acid solution and aqueous sodium hydrogencarbonate solution.

Subsequent flash chromatographic purification (petroleum ether/ diethyl ether = 1/2 (v/v)) gives an oil which is crystallised from diisopropyl ether to afford 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1-[2-((3-(trifluoromethyl)phenyl)sulfonyl)ethyl]-1H-pyrazole (0.52 gram, 19 % yield). Melting point: 118-119 °C.

In an analogous manner the compounds having formula (I) listed below have been prepared:

3-(4-Chlorophenyl)-1-[2-(benzylsulfonyl)ethyl]-4,5-dihydro-4-phenyl-1H-pyrazole.

Melting point: 161 °C.

3-(4-Chlorophenyl)-1-[2-((4-chlorophenyl)sulfonyl)ethyl]-4,5-dihydro-4-phenyl-1H-pyrazole. Melting point: Amorphous

3-(4-Chlorophenyl)-1-[2-((4-chlorophenyl)sulfonyl)ethyl]-4,5-dihydro-4-hydroxy-4-phenyl-1H-pyrazole. Melting point: 127-128 °C.

Example IX

N-[2-(3-(4-Chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazol-1-yl)ethyl]-3-(trifluoromethyl)benzenesulfonamide

Part A: A stirred solution of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (5.00 gram, 19.5 mmol) and N-(*tert*-butoxycarbonyl)aziridine (2.00 gram, 14.0 mmol) in toluene (100 ml) is heated at reflux temperature for 16 hours. After concentration *in vacuo* the residue is purified by flash chromatography (petroleum ether/ diethyl ether = 3/1 (v/v)), followed by petroleum ether/ diethyl ether = 1/1 (v/v)). After concentration *in vacuo* the remaining oily residue is crystallised from diisopropyl ether to afford 1-[2-((*tert*-butoxycarbonyl)amino)ethyl]-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (1.91 gram, 34 %). Repeated crystallisations from the mother liquor afforded an additional amount of crystalline 1-[2-((*tert*-butoxycarbonyl)amino)ethyl]-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (1.19 gram).

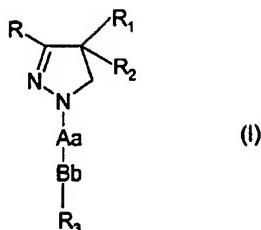
Part B: To a solution of 1-[2-((*tert*-butoxycarbonyl)amino)ethyl]-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (1.91 gram, 4.8 mmol) in dichloromethane (50 ml) is added trifluoroacetic acid (5 ml) and the resulting solution is stirred at room temperature for 5 hours. After concentration *in vacuo* the residue is dissolved in ethylacetate and washed with 2N sodium hydroxide solution. The ethyl acetate layer is dried over magnesium sulfate, filtered and

concentrated *in vacuo* to afford 1-(2-aminoethyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (1.44 gram, quantitative yield) as an oil.

Part C: To a solution of 1-(2-aminoethyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (0.56 gram, 1.87 mmol) and diisopropylethylamine in acetonitrile (20 ml) is added 3-(trifluoromethyl)phenylsulfonyl chloride (0.35 ml, 2.18 mmol) and the resulting solution is stirred at room temperature for 20 minutes. After concentration *in vacuo* the residue is dissolved in ethylacetate and washed with 2N sodium hydroxide solution. The ethylacetate layer is concentrated *in vacuo*. The resulting oil is crystallised from a small amount of diisopropyl ether to afford crystalline N-[2-(3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazol-1-yl)ethyl]-3-(trifluoromethyl)benzenesulfonamide (0.44 gram, 46 % yield). Melting point: 94-96 °C.

Claims

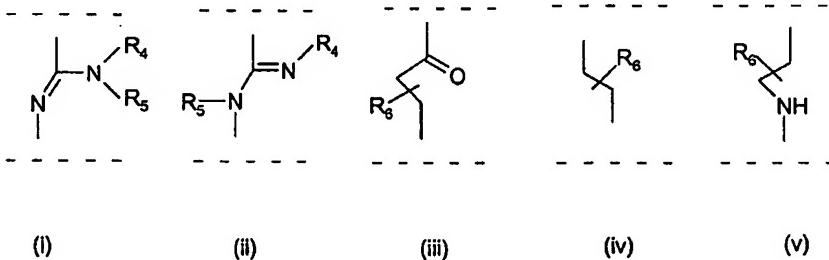
1. A compound of formula (I)



5

wherein

- R and R₁ are the same or different and represent phenyl, thienyl or pyridyl which groups may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, from the group C₁₋₃-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C₁₋₂)-amino, mono- or dialkyl (C₁₋₂)-amido, (C₁₋₃)-alkyl sulfonyl, dimethylsulfamido, C₁₋₃-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R and/or R₁ represent naphtyl,
 - R₂ represents hydrogen, hydroxy, C₁₋₃-alkoxy, acetoxy or propionyloxy,
 - Aa represents one of the groups (i), (ii), (iii), (iv) or (v)



20

wherein

- R_4 and R_5 independently of each other represent hydrogen or C_{1-8} branched or unbranched alkyl or C_{3-8} cycloalkyl or R_4 represents acetamido or dimethylamino or 2,2,2-trifluoroethyl or phenyl or pyridyl with the proviso that R_5 represents hydrogen
 - R_6 represents hydrogen or C_{1-3} unbranched alkyl

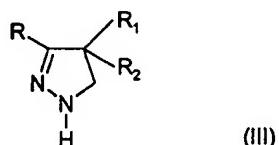
- Bb represents sulfonyl or carbonyl,
- 5 - R₃ represents benzyl, phenyl, thienyl or pyridyl which may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, or R₃ represents C₁₋₆ branched or unbranched alkyl or C₃₋₈ cycloalkyl, or R₃ represents naphtyl and tautomers, prodrugs and salts thereof.
- 10 2. A compound having formula (I) as claimed in claim 1, wherein R is the group 4-chlorophenyl, R₁ is phenyl, R₂ is hydrogen, Aa is the group (i) wherein R₄ is hydrogen and R₅ is methyl, Bb is sulfonyl, and R₃ represents 4-chlorophenyl, and salts thereof.
- 15 3. A pharmaceutical composition containing at least one compound as claimed in 1 as an active component.
4. A method of preparing pharmaceutical compositions characterized in that a compound as claimed in claim 1 is brought in a form suitable for 20 administration.
- 25 5. Process for the preparation of compounds having formula I, characterized in that
a) a compound is prepared wherein R, R₁-R₃ and Bb have the meanings given in claim 1 and Aa is a group of the formula (i) or (ii) as defined in claim 1 by
30 1) reacting a compound having formula (II) with hydrazine or hydrazine hydrate to obtain a compound having formula (III), which is reacted with a compound having formula (IVa) or (IVb) to give a compound having formula (V), which is reacted with a compound of the formula R₃-SO₂X or R₃-COX, wherein X is halogen, or
35 2) reacting a compound having formula (III) with a thioisocyanate of the formula (VI) to produce a compound of the formula (VII), which is reacted with an amine in the presence of a mercury (II) salt, or
3) reacting a compound having formula (III) with a compound of the formula

(VIII) to give a compound of the formula (IX) which is reacted with a halogenating agent to give a compound having formula (X) which is reacted with an amine, or

- 5 4) reacting a compound having formula (III) with a compound of the formula (XI) to give a compound having formula (XII) which is reacted with an amine, or
- 10 b) a compound is prepared wherein R, R₁-R₃ and Bb have the meanings given in claim 1 and Aa is a group of the formula (iii) or (iv) as defined in claim 1 by reacting a compound of the formula (III) with a compound of the formula (XIII) of (XIV), or.
- 15 c) a compound is prepared wherein R, R₁-R₃ and Bb have the meanings given in claim 1 and Aa is a group of the formula (v) as defined in claim 1, by reacting a compound having formula (III) with a compound having formula (XV) or (XVI) to give a compound having formula (XVII), which is deprotected to give a compound having formula (V), which is reacted with a compound having formula R₃-SO₂X or R₃-COX wherein X is halogen or with a compound of the formula R₃-COOH.

20

6. A compound of formula (III)

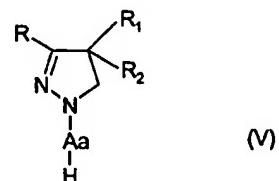


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wherein R₂ represents a hydroxy group and wherein R and R₁ have the meanings given in claim 1.

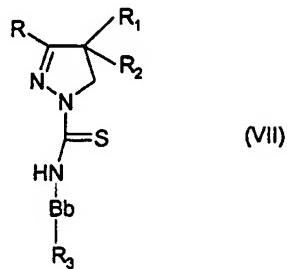
7. A compound of formula (V)

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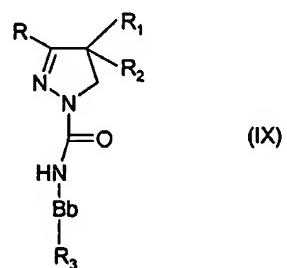
wherein Aa has the meaning (i), (ii) or (v) as given in claim 1 and wherein R, R₁ and R₂ have the meanings given in claim 1.

5 8. A compound of formula (VII)



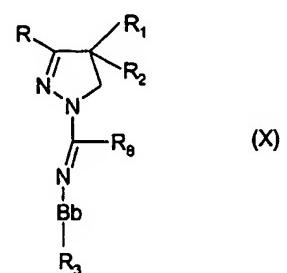
wherein R, R₁, R₂, R₃ and Bb have the meanings given in claim 1.

10 9. A compound of formula (IX)



15 wherein R, R₁, R₂, R₃ and Bb have the meanings given in claim 1.

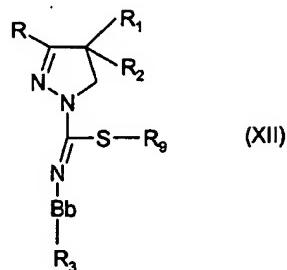
10. A compound of formula (X)



wherein R, R₁, R₂, R₃ and Bb have the meanings given in claim 1 and wherein R₈ represents a halogen atom.

11. A compound of formula (XII)

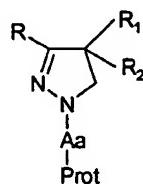
5



wherein R, R₁, R₂, R₃ and Bb have the meanings given in claim 1 and wherein R₈ represents a C₁₋₃ alkyl group.

10

12. A compound of formula (XVII)



(XVII)

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wherein R, R₁ and R₂ have the meanings given in claim 1 and wherein Aa has the meaning (v) as given in claim 1 and wherein Prot represents a so-called protective group.

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13. A method of treating psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite disorders, obesity, neurological disorders such as Parkinson's disease, dementia, dystonia, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, ischaemia, pain and other CNS-diseases involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.

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14. A method of treating gastrointestinal disorders involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.
- 5 15. A method of treating cardiovascular disorders involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/03247

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D231/06 C07D409/04 C07D401/04 A61K31/415 A61P25/04
 A61P9/00 C07D231/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

7 May 2001

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte 1st Application No

PCT/EP 01/03247

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